Defining Subgroups of Small-Cell Lung Cancer

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Small-cell lung cancer (SCLC) is a disease for which there has been no advance in systemic therapy for the past 30 years. In the background of this sobering data are many attempts to find targeted therapy that can have a real impact on patient outcome.[1] These attempts may have failed largely because of our inability to identify subgroups of SCLC patients who have an appropriate predictive biomarker for response. Thus, in this setting, investigators are attempting to define, similar to non–small-cell lung cancer (NSCLC), subgroups of SCLC which behave differently. This represents a departure from what has traditionally been viewed as a homogeneous disease. An obvious subgroup, representing approximately 1% of all SCLC, are patients with so-called "peripheral SCLC" which present with a solitary pulmonary nodule and whom are candidates for surgery.[2] Most genomic data published to date have focused on this group,[3,4] which has a very different clinical course than the classic SCLC we observe in everyday clinical practice. Another subgroup is the so-called "combined SCLC," previously called "mixed SCLC," which has histological features of both SCLC and NSCLC and may also behave differently.[5] This entity represents a fascinating disease because it puts into question the cellular origin of SCLC, which is an area of active investigation.[6,7]

With this knowledge, Varghese et al. are identifying yet another rare subgroup, SCLC patients who have never smoked. In our clinical practice, we have only seen three never-smoker patients with SCLC, and without epidermal growth factor receptor (EGFR) mutations, among 420 patients (0.7%) who are part of our ongoing clinicopathological SCLC database. Interest in this subgroup has mainly arisen from the observations that EGFR-mutant NSCLC patients treated with EGFR kinase inhibitors may transform into SCLC as a mechanism of resistance.[8] Because we are now routinely performing repeat biopsies on patients with EGFR mutation disease, this transformation is being seen on a much more common basis (3 patients in the past 4 months in our clinical practice alone). These patients seem to be somewhat more resistant to SCLC-directed therapy with initial impressions of lower response rates and shorter time to progression.

Multiple explanations for the occurrence of SCLC in never-smokers may be evoked. One explanation may simply be that it represents "an extrapulmonary SCLC," which may occur in people who have never smoked and can arise in various organs, including the gastrointestinal and genitourinary systems, but just happens to occur in the lung.[9] The causative factor for extrapulmonary SCLC remains unknown. Another putative explanation may be that SCLC of never-smokers may simply represent a dedifferentiation of a previously well-differentiated cancer, similar to what may be seen in prostate cancer transformation into small-cell variety after prolonged androgen ablation.[10] Indeed, we observed a case of NSCLC transforming into SCLC without EGFR tyrosine kinase inhibitor therapy. Another plausible explanation may be that we are really dealing with a "combined SCLC," but because of a paucity of biopsy material, only the SCLC part is being seen.[5] Yet another explanation is that the observed SCLC in the chest of a never-smoker may be a so-called "Askin tumor," a primitive neuroectodermal tumor of the Ewing family tumors. Although these are generally seen in children, adults can also be afflicted.[11] These rare, small, blue cell tumors can be

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diagnosed as SCLC in the adult population. We have recently seen a case in a 70-year-old light-smoker female who presented with SCLC. After sequencing the tumor, we discovered the classic fusion oncogene for Ewing's sarcoma, translocation of the Ewing sarcoma (EWS) gene on chromosome 22 to the Fli-1 proto-oncogene (FLI1) gene on chromosome 11, indicating most likely a tumor from the Ewing family. It is unclear whether this translocation was part of the mutation panel used in the study by Varghese et al. Finally, a simple explanation may be related to the use of self-administered smoking history questionnaires, which have always been criticized.

The study by Varghese et al. also highlights the difficulties in obtaining tissue from SCLC patients for genomic analyses. Indeed, in their series, only two patients had enough tissue for targeted next-generation sequencing. The group at Memorial Sloan Kettering Cancer Center should be commended for their persistent efforts to further define and understand a disease for which therapeutic progress is long overdue.

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